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Diseases of the Colon & Rectum

Pathologic Determinants of Survival After Resection of T3N0 (Stage IIA) Colorectal Cancer: Proposal for a New Prognostic Model

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PURPOSE: There is an increasing need for accurate prognostic stratification of patients with Stage II colorectal cancer to identify a subgroup of high-risk patients who may benefit from adjuvant therapies. This study was designed to evaluate the prognostic impact of a wide spectrum of pathologic parameters in a consecutive series of homogenously treated and well-characterized patients with Stage IIA (T3N0M0) colorectal cancer. METHODS: The study included 238 patients operated on by a single surgeon for Stage IIA colorectal tumors. The median postoperative follow-up was 110 (range, 96–120) months. At least 12 lymph nodes were harvested and examined in all the resection specimens. The prognostic value of 13 pathologic parameters, including lymph node occult disease (micrometastases) detected by immunohistochemistry, was investigated. RESULTS: Multivariate analysis identified tumor growth pattern (expanding or infiltrating; $P = 0.01$) and extent of tumor spread beyond muscularis propria (≤5 mm or >5 mm; $P = 0.04$) as the only factors having independent prognostic value. The combination of these two easily determined parameters allowed us to identify two groups of patients at low risk or high risk of tumor recurrence. The eight-year survival rates were 83.3 and 53.4 percent for the two groups, respectively. The high-risk group comprised those patients with infiltrating tumors and extramural tumor spread > 5 mm. CONCLUSIONS: We propose a new and simple prognostic model to identify patients with high-risk Stage IIA colorectal cancer for whom adjuvant therapies may be justified and effective. [Key words: Colorectal cancer; Prognosis; Lymph node micrometastases; Pathologic parameters]

The Dukes staging system was proposed more than 70 years ago and, since then, has been the most widely employed prognostic classification after surgery for colorectal cancer.[1] This staging system is composed of two fundamental parameters, tumor penetration of the bowel wall and lymph node (LN) involvement. Although several alternative pathologic and molecular prognostic factors have been proposed in recent years, these two parameters remain the most powerful prognostic indicators.[2] In particular, LN status is considered the most important determinant of the decision to institute postoperative therapies in both colon and rectal cancer. However, one major flaw of the Dukes classification is that a great proportion of colorectal carcinomas, approximately 40 to 50 percent in most series, are classified

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as Dukes B, *i.e.*, tumors extending beyond the wall with negative LNs.[3–6] Unfortunately, this is a broad category with respect to patient clinical outcome with a reported five-year survival rate ranging between 60 and 75 percent.[3–7] This is primarily caused by the fact that Dukes B Stage encompasses a wide spectrum of disease, from early penetration through the bowel wall to extensive tumors with involvement of the serosa, surgical margins, or adjacent organs. Therefore, there is a need to better predict the prognosis of these patients.

The recently revised American Joint Committee on Cancer (AJCC) sixth edition cancer staging system[8] has stratified Stage II, *i.e.*, Dukes B Stage, into two subsets—Stage IIA and Stage IIB—on the basis of whether the tumor is T3 or T4, respectively. Tumors classified as Stage IIA, *i.e.*, invading through the muscularis propria into the subserosa or nonperitonealized pericolic/perirectal tissues, have a significantly better prognosis than Stage IIB tumors, which directly invade the peritoneum or other organs/structures.[9] A possible explanation for this finding is that Stage IIB tumors may not have received proper *en bloc* surgical resection, so that residual disease was not excised.[9]

Recently, several clinical studies have addressed the issue of whether tumor relapse in Stage II tumors is related, at least in part, to the presence of LN occult metastases, *i.e.*, single tumor cells or cell clusters, which are not revealed by routine hematoxylin-eosin staining of histology sections.[10–16] Unfortunately, previously reported results on the prognostic and clinical impact of LN occult tumor cells, identified by immunohistochemistry or reverse transcriptase-polymerase chain reaction, are controversial.[10–16] This discrepancy may be the result of the fact that the majority of published studies have not subdivided nodal occult tumor cells into micrometastases (MCM) or isolated tumor cells on the basis of their dimensions as recently recommended by the new TNM-AJCC classification.[8] Isolated tumor cells are classified as single tumor cells or cell clusters measuring < 0.2 mm and are given a pN0 designation because their prognostic significance is still undetermined.[17] MCM are defined as clusters of cells that measure > 0.2 mm but < 2.0 mm and are designated by pN1 (mi) because they have shown potential malignant capability.[17]

This study was designed to evaluate the prognostic impact of a wide spectrum of pathologic parameters, including LN MCM, in a large series of patients curatively operated on for Stage IIA colorectal cancer. In particular, our goal was to identify a subset of patients at high risk of tumor recurrence for whom adjuvant chemotherapy may be of benefit.

PATIENTS AND METHODS

Between 1988 and 1997, a total of 587 consecutive patients underwent potentially curative resection of colorectal tumors by the same surgeon (CC) at the Department of General Surgery, University of Florence, Italy; 238 patients had tumors classified as Stage IIA (T3N0M0), according to the sixth edition of the AJCC staging system,[8] and were included in the study (131 males; 55 percent; median age, 67 (range, 38–88) years). Cases with synchronous or metachronous tumors, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer were excluded. Tumor distribution was as follows: 68 (28.6 percent) in the proximal colon (up to the splenic flexure), 90 (37.8 percent) in the distal colon (up to the end of sigmoid colon), and 80 (33.6 percent) in the rectum. Surgical resection was defined as radical when there was no evidence of distant metastases and the clearance of the tumor was complete, both macroscopically and histologically. Complete circumferential excision of the mesorectum was performed in all patients with tumors of the middle and lower rectum. Both the longitudinal and radial margins of all resected specimens were microscopically free of tumor. A distal clearance of at least 2 cm of healthy mucosa from the lower edge of the tumor was provided in all patients. Each patient was followed up for at least eight years (median value, 110 (range, 96–120) months) or until death. Only deaths attributable to recurrent cancer were counted as events in the process of survival evaluation. All surviving patients had been thoroughly informed about the study and gave written consent for the investigation in accordance with the ethical guidelines of our university. No patient received preoperative or postoperative radiotherapy or chemotherapy.

Pathologic Evaluation

The resection specimens were fixed in 10 percent buffered formalin for 24 hours and an adequate number of sections was sampled from each tumor (mean, 6 (range, 4–12) sections) for microscopic examination. All tissue sections were embedded in paraffin and stained with hematoxylin-eosin. The mesocolic/mesorectal fat was dissected meticulously

by using a manual technique, and a median of 18 LNs (range, 12–42) was harvested and examined per tumor specimen. Cases with fewer than 12 LNs examined or showing tumor nodules with LN-like shape in the peri-intestinal fat were excluded from the study. Lymph nodes were bisected and three consecutive 5–μm-thick sections were cut from each paraffin wax block containing LNs. The original histologic slides of both the tumors and LNs were reviewed by the same pathologist (LM), who had no knowledge of each patient's outcome. All cases were confirmed to be free of LN metastases.

Tumor morphology and size were ascertained from the original pathologic reports. Tumor morphology was classified as exophytic or nonexophytic. We categorized tumor size into two groups, ≤5 cm and >5 cm, on the basis of the mean value of the maximum diameter of the tumors. Microscopic assessment included the recording of tumor histotype, tumor grade, tumor growth pattern, peritumoral lymphocytic infiltrate, desmoplastic response, Crohn's-like lymphoid reaction, involvement of extramural veins and lymphatic vessels, and extent of tumor spread beyond muscularis propria. Tumors were classified as mucinous or nonmucinous, according to the amount of the mucinous component (respectively, more or less than 50 percent of tumor volume). Tumor grade was categorized as low grade, including well or moderately differentiated carcinomas, and high grade, including poorly differentiated, undifferentiated, and mucinous cancers.

The pattern of tumor growth, expanding or infiltrating, was assessed according to criteria defined by Jass *et al.*[18] In particular, the growth pattern was classified as expanding when advancement of the tumor was clearly evident and the tumor had pushed into the surrounding tissues, thus creating a well-delineated border. It was defined as infiltrating when the tumor dissected the muscularis propria and peri-intestinal tissues with small glands or irregular clusters or cords of cells without a distinct border. Peritumoral lymphocytic infiltrate was defined as conspicuous when there was a distinctive cuff of lymphocytes at the invasive margin of tumor growth or as little/absent when the lymphocytic cuff was not present, in accordance with criteria set by Jass *et al.*[18] Desmoplasia was evaluated at the advancing edge of the tumor and categorized as extensive when most of the tumor area was surrounded by fibrosis or as nonextensive in the remaining cases, according to the criteria defined by Halvorsen and Seim.[19] Crohn's-like lymphoid reaction at the invasive margin of the tumors was classified as absent or present according to the criteria established by Harrison *et al.*[20] Involvement of extramural veins and lymphatic vessels was assessed according to the criteria of Talbot *et al.*[21] The extent of tumor spread was determined as a measurement from the outer border of the longitudinal muscle layer to the most distant point of tumor spread and divided into two groups: slight/moderate if ≤ 5 mm, and extensive if > 5 mm.

To allow the maximal standardization and reproducibility of our results, pathologic evaluation of all these parameters was reviewed according to the guidelines recently proposed by the Colorectal Working Group of the AJCC.[22]

Immunohistochemical Staining and Lymph Node Micrometastases Definition

For each case, 12 new serial 5–μm-thick sections were obtained from the original paraffin blocks of the recovered LNs and were mounted on microscope slides. Staining procedures were conducted by using an automated immunostainer (Ventana NexES®; Ventana Medical Systems, Tucson, AZ). Sections were deparaffinized in xylene and rehydrated in a descending ethanol series. Microwave-based heat-induced epitope retrieval was performed. Endogenous peroxidase activity was blocked by immersion for ten minutes in 0.3 percent hydrogen peroxide in methanol solution, followed by a single wash in phosphate-buffered saline (PBS; pH 7.4). Sections were incubated with the monoclonal antibody anti-cytokeratin 20 (CK20) (clone Ks20.8®, Cell Marque Corporation, Hot Springs, AR). The immunostaining was developed by using 3,3′-diaminobenzidine as chromogen. Appropriate positive and negative controls were added on each automated immunohistochemistry run to confirm the sensitivity and specificity of the antibody (sections of CK20-positive CRC tissue served as positive controls; negative controls were obtained by omitting the primary antibody). The immunostained slides were evaluated by the same pathologist (LM), who had no knowledge of pathologic data or each patient's outcome.

Clusters of cells detected by CK20 immunostaining were considered as metastases only when they showed unequivocal morphologic features of cancer cells. According to the sixth edition of the TNM system by the AJCC,[8] immunostained tumor cells

found in LNs were classified as MCM only when tumor deposits measured > 0.2 mm but < 2.0 mm (Fig. 1).

Statistical Analysis

Survival time was calculated from the date of surgery to the date of death or last follow-up. The relationship between pathologic variables and survival was estimated by using the Kaplan-Meier method.[23] Differences among the survival curves were tested for statistical significance with the help of the log-rank test. The Cox proportional hazard regression model[24] was used to identify the pathologic factors that could independently influence survival. STATA® Statistical Software release 6.0 (College Station. TX) was used for all the analyses. $P < 0.05$ was considered significant.

RESULTS

Pathologic data regarding the 238 patients are summarized in Table 1. At the time of analysis, no patients were lost to follow-up and there had been 53 cancer-related deaths. Among these, 46 were caused by distant metastases and 7 by locoregional recurrence after resection of rectal tumors. When all 238 patients were considered, the eight-year survival rate was 77.3 percent (Fig. 2). Intraobserver agreement on growth pattern and lymphocytic infiltrate evaluation were evaluated in 85 patients by measuring the κ coefficient. These patients were examined for the first time by our pathologist (LM) in 2002[5] and then reevaluated for the present study. The κ value reached 0.91 and 0.82 for the two parameters, respectively, thus demonstrating almost perfect agreement.

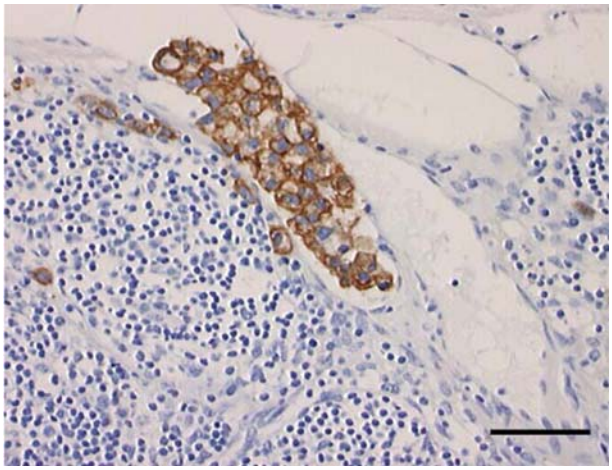

Figure 1. Immunohistochemical staining for cytokeratin 20 (CK20). A cluster of CK20-positive cells classified as micrometastasis (>0.2 mm and ≤2 mm) was detected in the peripheral sinus of a lymph node (original magnification × 200; bar = 100 μm).

Among the pathologic parameters estimated, tumor growth pattern, Crohn's-like lymphoid reaction, extent of spread beyond muscularis propria, and LN MCM were shown to be significantly correlated to patient survival according to univariate analysis (Table 2). Survival was analyzed within each group of patients with different tumor location: the prognostic value of all the pathologic features did not significantly differ between patients with colon and those with rectal tumors (data not shown). Among the four prognostic parameters, Cox regression analysis selected the growth pattern and the extent of spread beyond muscularis propria as having an independent prognostic value (Table 3). On the basis of this result, patients were classified into four groups considering all the possible combinations of the two independent prognostic factors. No significant differences in median age, male/female ratio, and tumor location were found among the four subsets (data not shown). The survival rates of these groups were evaluated and compared (Table 4). Those patients with tumors having an infiltrating growth pattern in combination with extensive extramural spread showed a 53.4 percent eight-year survival rate, whereas the other three groups, when pooled together, showed a comprehensive eight-year survival rate of 83.3 percent. Therefore, two distinct groups—high-risk and low-risk—with a significant difference in survival rates ($P < 0.0001$) were identified (Fig. 3).

DISCUSSION

Patients with Stage II colorectal cancer show the highest variability in clinical outcome with their five-year survival rate ranging between 60 and 75 percent.[3–6] The use of adjuvant therapy in these patients remains controversial,[25–28] and increasing attention is being focused on the identification of new factors, which may enable a more accurate patient prognostic stratification within this stage. According to recommendations of the new AJCC sixth cancer staging edition,[8] recent studies have demonstrated that patients with Stage IIB (T4N0) tumors have a significantly worse prognosis than patients with Stage IIA (T3N0) tumors,[9] suggesting

Table 1.
Categorization of Pathologic Parameters in 238 Patients with Stage IIA Colorectal Cancer

Parameter	No. of Patients (%)
Tumor morphology	
Exophytic	107 (45)
Nonexophytic	131 (55)
Maximum diameter of tumor (cm)	
≤5	113 (47.5)
>5	125 (52.5)
Tumor type	
Mucinous	34 (14.3)
Nonmucinous	204 (85.7)
Tumor grade	
High	78 (32.8)
Low	160 (67.2)
Growth pattern	
Expanding	87 (36.6)
Infiltrating	151 (63.4)
Peritumoral lymphocytic infiltrate	
Little/absent	192 (80.7)
Conspicuous	46 (19.3)
Desmoplastic response	
Nonextensive	189 (79.4)
Extensive	49 (20.6)
Crohn's-like lymphoid reaction	
Present	69 (29)
Absent	169 (71)
Venous invasion	
Present	56 (23.5)
Absent	182 (76.5)
Lymphatic vessel invasion	
Present	53 (22.3)
Absent	185 (77.7)
Extent of spread	
Slight/moderate	156 (65.5)
Extensive	82 (34.5)
Lymph node micrometastases	
Present	20 (8.4)
Absent	218 (91.6)

that patients classified as Stage IIB may benefit from adjuvant therapies. Based on these results, our study exclusively focused on patients classified as Stage IIA to identify new subgroups of patients at high risk of tumor relapse by analyzing the actual prognostic impact of a wide spectrum of pathologic parameters.

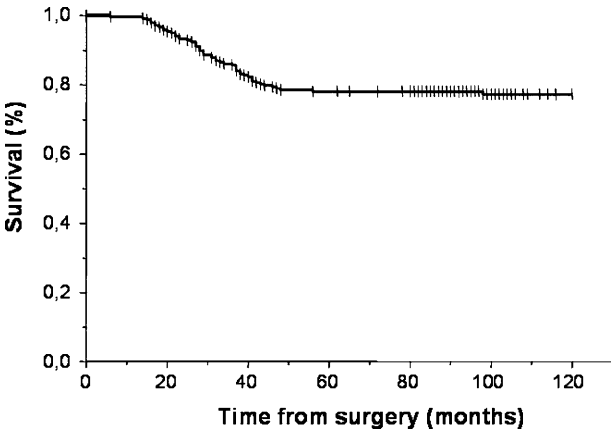

Figure 2. Kaplan-Meier survival curve of 238 patients with Stage IIA colorectal cancer.

A pivotal step in classifying a tumor as Stage II is the accuracy of LN harvesting and examination. The AJCC recommends that a minimum of 12 LNs be examined to accurately predict node negativity in colorectal cancer, and recent studies have shown that the five-year survival rate of patients classified as Stage II progressively increases with the number of nodes examined.[29] If few lymph nodes are examined, there is an increased risk that at least one metastatic LN is missed in the resected specimen and thus, a patient who is truly Stage III is mistakenly classified as Stage II.[5,30] As a consequence, we included in the present study only those patients with at least 12 harvested and examined LNs, reaching a median value of 18 LNs sampled when all 238 patients were considered. To both improve accuracy of pathologic examination and evaluate the potential

Table 2.
Univariate Analysis of Pathologic Parameters in 238 Patients with Stage IIA Colorectal Cancer

Parameter	Eight-Year Survival (%)	*P* Value
Tumor site		0.31
Proximal colon	82.3	
Distal colon	78.8	
Rectum	72.5	
Tumor morphology		0.22
Exophytic	81.3	
Nonexophytic	74.8	
Maximum diameter of tumor (cm)		0.1
≤5	82.3	
>5	73.6	
Tumor type		0.12
Mucinous	67.6	
Nonmucinous	79.4	
Tumor grade		0.12
High	71.7	
Low	80.5	
Growth pattern		0.01
Expanding	86.2	
Infiltrating	72.8	
Peritumoral lymphocytic infiltrate		0.19
Little/absent	84.7	
Conspicuous	76	
Desmoplastic response		0.29
Nonextensive	79.3	
Extensive	71.4	
Crohn's-like lymphoid reaction		0.03
Present	86.7	
Absent	73.9	
Venous invasion		0.4
Present	81.8	
Absent	76.3	
Lymphatic vessel invasion		0.44
Present	73.5	
Absent	78.9	
Extent of spread		0.008
Slight/moderate	82.6	
Extensive	68.2	
Lymph node micrometastases		0.03
Present	60	
Absent	79.3	

prognostic impact of nodal occult metastases in our patients, we investigated the presence of nodal CK20-positive tumor cells missed during routine hematoxylin-eosin staining. We considered as true MCM only those tumor cell clusters that measured > 0.2 mm but < 2.0 mm. MCM have been shown to be the only type of nodal occult disease to have metastatic activities, such as cell proliferation, stromal reaction, or extravasation,[17] and are designated as pN1 (mi) by the most recent TNM-AJCC classification.[8] Our survival analysis confirmed this datum, showing a worse prognosis in patients with MCM than in those without them. However, the presence of MCM did not show an independent effect on survival at multivariate

Table 3.
Multivariate Analysis of Prognostic Factors Using Cox Proportional Hazard Regression Model

Prognostic Factors	Comparison	Hazards Ratio (95% CI)	*P* Value
Growth pattern	Infiltrating *vs.* expanding	2.24 (1.18–4.286)	0.01
Crohn's-like lymphoid reaction	Absent *vs.* present	1.8 (0.873–3.728)	0.1
Extent of spread beyond muscularis propria	Extensive *vs.* slight/moderate	1.95 (1.134–3.38)	0.04
Lymph node micrometastases	Present *vs.* absent	1.6 (0.731–3.507)	0.23

Table 4.
Prognostic Grouping of 238 Patients with Stage IIA Colorectal Cancer According to the Combination of Tumor Growth Pattern and Extent of Spread Beyond Muscularis Propria

Prognostic Factors	No. of Patients (%)	Eight-Year Survival (%)
Expanding and slight/moderate spread	56 (23.5)	87.5
Expanding and extensive spread	31 (13)	83.8
Infiltrating and slight/moderate spread	100 (42)	80.9
Infiltrating and extensive spread	51 (21.5)	53.4

analysis. This is probably the result of the relatively low incidence (8.4 percent) of MCM in our series of patients, despite the high number of both LNs and nodal cut sections examined.

In clinical practice, the more independent prognostic factors we have, the more accurately we can predict the clinical outcome of patients. We investigated the prognostic significance of a large number of pathologic parameters and identified two of them as having an independent predictive value according to multivariate analysis. Tumor growth pattern was first proposed by Jass *et al.*[18] in their prognostic classification of rectal tumors in conjunction with peritumoral lymphocytic infiltration, tumor spread, and lymph node involvement. Although Jass' new grading system was shown to have superior prognostic value to Dukes staging, it has not been recommended for routine usage in standard reporting protocols because some studies have raised the criticism of poor reproducibility and reliability of the growth pattern and lymphocytic infiltrate.[20,31,32] In two previously published studies, we have shown the lack of any prognostic significance of lymphocytic infiltrate but a strong correlation between tumor growth pattern and survival in patients with LN-negative and patients with LN-positive colorectal cancer.[3,33] In the present study, we reconfirmed these data in patients classified as Stage IIA, thus demonstrating, in accordance with the experience of other authors,[2,34–37] the reliability of the growth pattern as an objective predictor of prognosis. In particular, the College of American Pathologists Consensus Statement in 1999[2] stated that the potential subjective character of this promising prognostic factor can be maximally reduced if its assessment rigorously follows the definitions published by Jass *et al.*[18]

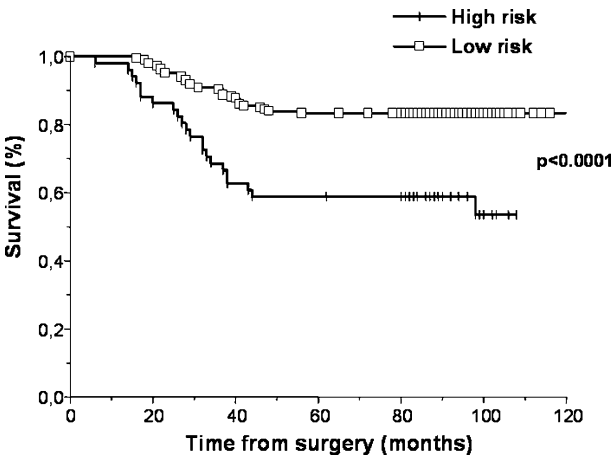

Figure 3. Kaplan-Meier survival curves of low-risk and high-risk patients with Stage IIA colorectal cancer.

The strong correlation between the pattern of tumor growth and clinical outcome may be explained by the biologic relationship of this parameter with the nature of the advancing tumor margin, which is considered the most representative area of the tumor aggressiveness. In fact, the pivotal steps in local invasion and metastasis of a solid tumor are considered to be both dissociation and migration of neoplastic cells out of the main tumor at the invasive front.[38] The evaluation of growth pattern most likely reflects these tumor characteristics.

The other independent prognostic factor that emerged from our survival analysis is the extent of tumor spread beyond the muscularis propria, that is, spread into the subserosa for colon and intraperitoneal rectal cancer or into the mesorectum for extraperitoneal rectal tumors. It is worth emphasizing that subserosal involvement is not synonymous with peritoneal involvement; subserosa and serosa are two distinct tissue layers.[39] As mentioned earlier, peritoneal involvement has been shown to be a strong, independent, prognostic factor in colon cancer[4,6] and has been designated with the major local tumor stage categorization of T4 by the AJCC.[8] The unfavorable prognosis linked to serosal invasion is most likely the result of the high probability of tumor transcoelomic dissemination at the time of surgery[6,9,39] and, thus, to incomplete tumor removal. However, our finding of a significantly worse prognosis for patients with extensive extramural spread (>5 mm) compared with those with slight/moderate spread (≤5 mm) may be ascribed to a diffuse

invasion of the blood/lymphatic vessels and nerve fibers that are abundantly present within extramural soft tissue. This implies a high risk for developing hematogenous metastases or locoregional recurrence.

Although the prognostic importance of venous and lymphatic invasion by tumor has been strongly suggested in the literature,[2] we did not find any correlation between these two parameters and the clinical outcome of our patients. Most studies reporting a prognostic value for venous invasion included patients with Stage I to Stage IV colorectal cancer.[2] However, at least four previously published studies failed to show any prognostic impact of venous invasion in patients with Stage II colorectal cancer.[40–43] It might be hypothesized that invasion of blood vessels, especially large extramural veins, is a late event in the process of tumor spread and thus is prognostically relevant only in patients with tumors at advanced stage or with proven ability to establish metastases. As for lymphatic invasion, its prognostic significance has been reported to be linked to lymph node metastasis prediction.[44] The exclusion of potentially understaged patients (*i.e.*, those with < 12 lymph nodes examined in the surgical specimen) and the low incidence of micrometastases may explain the lack of any predictive value of this parameter in our series of patients.

Interestingly, we found that growth pattern and extent of local spread can be effectively combined to provide a robust and simple prognostic model. We were able to divide patients into two categories with a low risk or high risk of tumor-related death. The low-risk group resulted from the combination of both patients with expanding tumors, independently of the extent of tumor spread, and patients with infiltrating tumors but slight/moderate spread. These patients showed similar prognoses and a cumulative 83.3 percent eight-year survival rate. Although our analysis was not comprehensive of all the possible pathologic determinants of tumor aggressiveness reported in the literature, the ≈16 percent incidence of disease relapse in this low-risk group is most likely caused by potential patient-related factors, such as a deficiency in the immune response against the tumor. The high-risk group comprised those patients with infiltrating tumors and extensive tumor spread, showing a cumulative 53.4 percent eight-year survival rate. This rate is similar to that reported in previous studies for patients with Stage III or Dukes C, *i.e.*, those with metastatic lymph nodes.[5,9,45] As a consequence, the administration of adjuvant therapy may be justified and effective in this class of patients.

CONCLUSIONS

We investigated the predictive value of a wide spectrum of pathologic parameters in a large series of homogenously treated and characterized patients with Stage IIA colorectal patients. Our survival analysis identified both the growth pattern and extent of local tumor spread as having independent prognostic value. By combining these two easily determined parameters, we were able to elaborate a new and simple prognostic classification that could help to identify a subset of patients with poor outcome who may then benefit from adjuvant therapies. However, future clinical trials using multicenter patient cohorts should be prospectively performed to evaluate the reproducibility of our results and the opportunity of using this prognostic model in routine practice.

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REFERENCES

1. Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol 1932;35:323–32.
2. Compton CC, Fielding LP, Burgart LJ, *et al*. Prognostic factors in colorectal cancer: College of American Pathologists consensus statement 1999. Arch Pathol Lab Med 2000;124:979–94.
3. Cianchi F, Messerini L, Palomba A, *et al*. Character of the invasive margin in colorectal cancer: does it improve prognostic information of Dukes staging? Dis Colon Rectum 1997;40:1170–6.
4. Petersen VC, Baxter KJ, Love SB, *et al*. Identification of objective pathological prognostic determinants and models of prognosis in Dukes' B colon cancer. Gut 2002;51:65–9.
5. Cianchi F, Palomba A, Boddi V, *et al*. Lymph node recovery from colorectal tumor specimens: recommendation for a minimum number of lymph nodes to be examined. World J Surg 2002;26:384–9.
6. Shepherd NA, Baxter KJ, Love SB. The prognostic importance of peritoneal involvement in colonic cancer: a prospective evaluation. Gastroenterology 1997;112:1096–102.
7. Burdy G, Panis Y, Alves A, *et al*. Identifying patients with T3-T4 node-negative colon cancer at high risk of recurrence. Dis Colon Rectum 2001;44:1682–8.
8. Greene FL, Page DL, Fleming ID, *et al*. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag, 2002.

9. O'Conell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer Sixth Edition Staging. J Natl Cancer Inst 2004;96:1420–5.
10. Öberg A, Stenling R, Tavelin B, *et al*. Are lymph node micrometastases of any clinical significance in Dukes Stages A and B colorectal cancer? Dis Colon Rectum 1998;41:1244–9.
11. Isaka N, Nozue M, Doy M, *et al*. Prognostic significance of perirectal lymph node micrometastases in Dukes' B rectal carcinoma: an immunohistochemical study by CAM5.2. Clin Cancer Res 1999;5:2065–8.
12. Tschmelitsch J, Klimstra DS, Cohen AM. Lymph node micrometastases do not predict relapse in Stage II colon cancer. Ann Surg Oncol 2000;7:601–8.
13. Andreola S, Leo E, Belli F, *et al*. Adenocarcinoma of the lower third of the rectum: metastases in lymph nodes smaller than 5 mm and occult micrometastases; preliminary results on early tumor recurrence. Ann Surg Oncol 2001;8:413–7.
14. Yasuda K, Adachi Y, Shiraishi N, *et al*. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. Ann Surg Oncol 2001;8:300–4.
15. Feezor RJ, Copeland EM, Hochwald SN. Significance of micrometastases in colorectal cancer. Ann Surg Oncol 2002;9:944–53.
16. Kronberg U, López-Kostner F, Soto G, *et al*. Detection of lymphatic micrometastasis in patients with Stages I and II colorectal cancer: impact on five-year survival. Dis Colon Rectum 2004;47:1151–7.
17. Hermanek P, Hutter RV, Sobin LH, Wittekind C. Classification of isolated tumor cells and micrometastases. Cancer 1999;15:2668–73.
18. Jass JR, Love S, Northover JM. A new prognostic classification for rectal cancer. Lancet 1987;1:1303–6.
19. Halvorsen TB, Seim E. Association between invasiveness, inflammatory reaction, desmoplasia and survival in colorectal cancer. J Clin Pathol 1989;42:162–6.
20. Harrison JC, Dean PJ, El-Zeky F, *et al*. From Dukes through Jass: pathological prognostic indicators in rectal cancer. Hum Pathol 1994;25:498–505.
21. Talbot IC, Ritchie S, Leighton M, *et al*. Invasion of veins by carcinoma of rectum: method of detection, histological features and significance. Histopathology 1981;5:141–63.
22. Compton C, Fenoglio-Preiser CM, Pettigrew N, Fielding LP. American Joint Committee on Cancer Prognostic Factors Consensus Conference. Colorectal Working Group Cancer 2000;88:1739–57.
23. Kaplan E, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
24. Cox DR. Regression model and life tables. J R Stat Soc 1972;(B)34:187–220.
25. Anonymous. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995;345:939–44.
26. Wolmark N, Rockette H, Fisher B, *et al*. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993;11:1879–87.
27. Mamounas E, Wieand S, Wolmark N, *et al*. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four national surgical adjuvant breast and bowel project adjuvant studies (C-01, C-02, C-03 and C-04). J Clin Oncol 1999;17:1349–60.
28. Anonymous. Intranational Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J Clin Oncol 1999;17:1356–68.
29. Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. Am J Surg Pathol 2002;26:179–89.
30. Caplin S, Cerottini JP, Bosman FT, Constanda MT, Givel JC. For patients with Dukes' B (TNM Stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. Cancer 1998;83:666–72.
31. Deans GT, Heatley M, Anderson N, *et al*. Jass' classification revisited. J Am Coll Surg 1994;179:11–7.
32. Jass JR, Ajioka Y, Allen JP, *et al*. Assessment of invasive growth pattern and lymphocytic infiltration in colorectal cancer. Histopathology 1996;28:543–8.
33. Cianchi F, Palomba A, Messerini L, *et al*. Tumor angiogenesis in lymph-node negative rectal cancer: correlation with clinicopathological parameters and prognosis. Ann Surg Oncol 2002;9:20–6.
34. Fisher ER, Robinsky B, Sass R, *et al*. Relative prognostic value of the Dukes and the Jass systems in rectal cancer: findings from the National Surgical Adjuvant Breast and Bowel Projects (Protocol R-01). Dis Colon Rectum 1989;32:944–9.
35. Dundas SA, Laing RW, O'Cathain A, *et al*. Feasibility of new prognostic classification for rectal cancer. J Clin Pathol 1988;41:1273–6.
36. Shepherd NA, Saraga E-P, Love SB, Jass JR. Prognostic factors in colonic cancer. Histopathology 1989; 14:613–30.
37. Ponz de Leon M, Sant M, Micheli A, *et al*. Clinical and pathologic prognostic indicators in colorectal cancer: a population-based study. Cancer 1992;69:626–35.
38. Gabbert H. Mechanism of tumor invasion: evidence from in vivo observations. Cancer Metastasis Rev 1985;4:293–309.
39. Ludeman L, Shepherd NA. Serosal involvement in gastrointestinal cancer: its assessment and significance. Histopathology 2005;47:123–31.

40. Khankhanian N, Mavligit GM, Russell WO, Schimek M. Prognostic significance of vascular invasion in colorectal cancer of Dukes' B class. Cancer 1977;39:1195–200.
41. Minsky BD, Mies C, Rich TA, Recht A, Chaffey JT. Potentially curative surgery of colon cancer: the influence of blood vessel invasion. J Clin Oncol 1988;6:119–27.
42. Mulcahy HE, Toner M, Patchett SE, Daly L, O'Donoghue DP. Identifying Stage B colorectal cancer patients at high risk of tumor recurrence and death. Dis Colon Rectum 1997;40:326–31.
43. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001;16:305–6.
44. Brodsky JT, Richard GK, Cohen AM, Minsky BD. Variables correlated with the risk of lymph node metastasis in early rectal cancer. Cancer 1992;15:322–6.
45. Wolmark N, Fisher B, Wieand HS. The prognostic value of the modifications of the Dukes' C class of colorectal cancer. Ann Surg 1986;203:115–22.